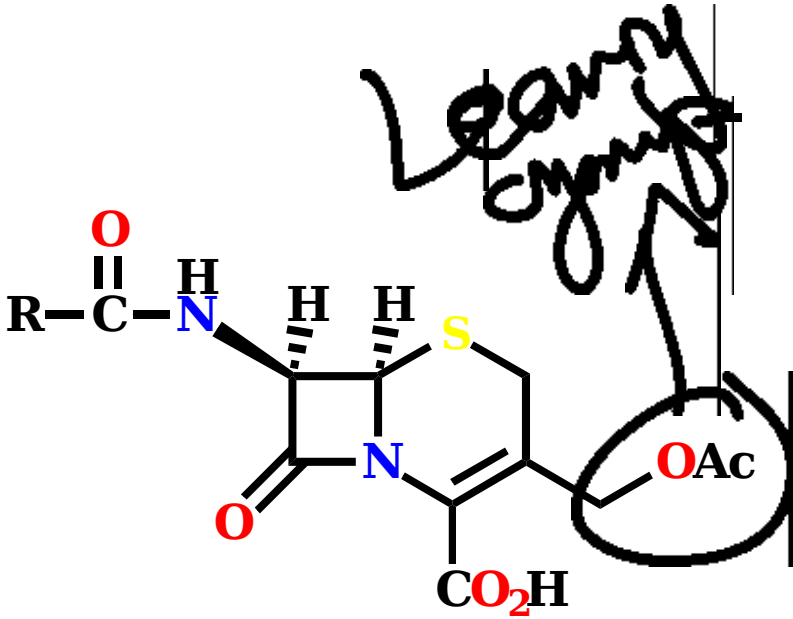
An Introduction to Chemical Basis of Action II

ANTIBACTERIAL AGENTS

Part 2: Cephalosporins

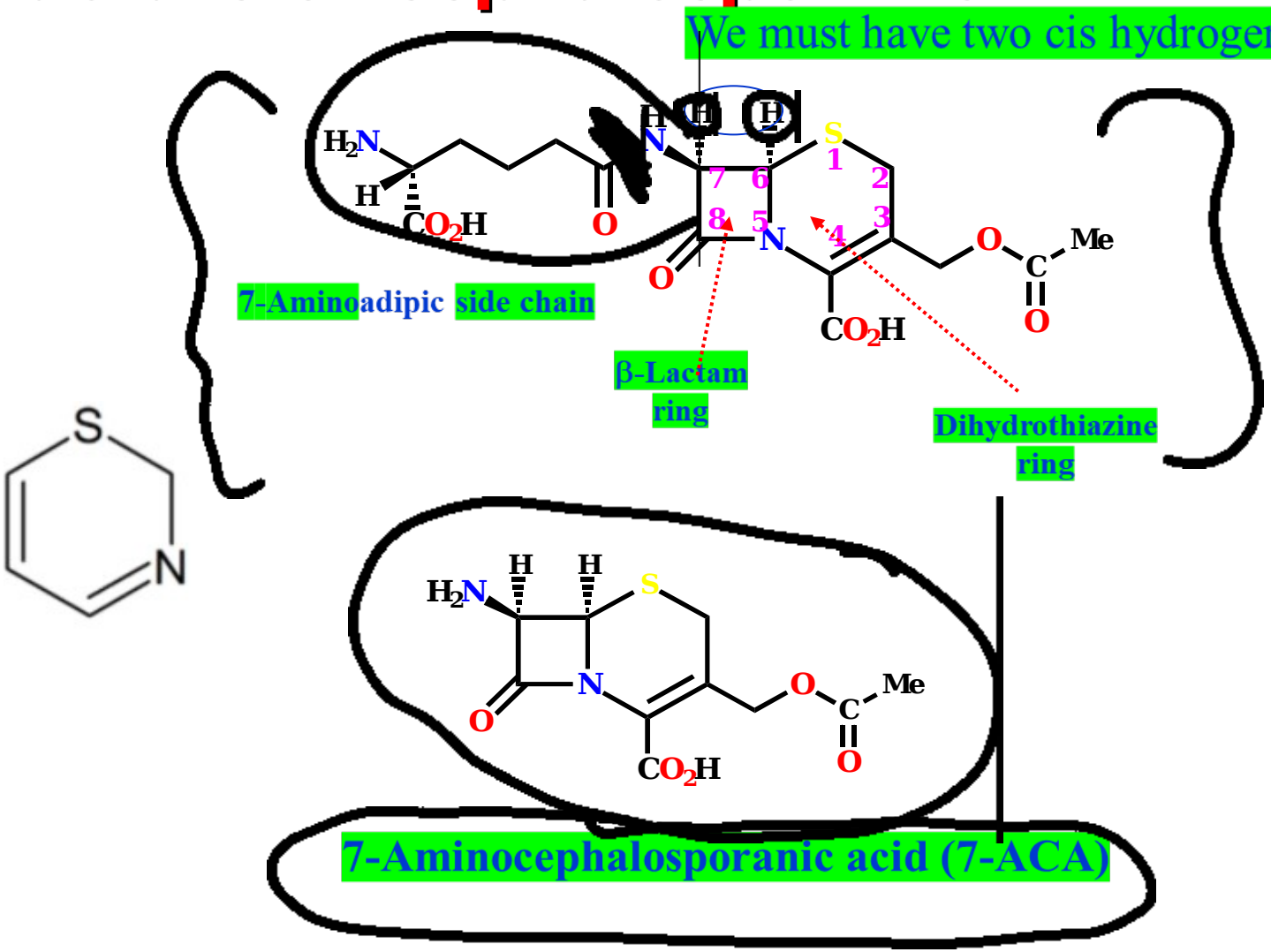
1. Introduction

- **Antibacterial agents which inhibit bacterial cell wall synthesis**
- **Discovered from a fungal colony in Sardinian sewer water (1948)**
- **Cephalosporin C identified in 1961**

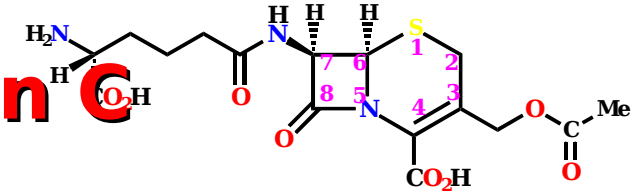


B-lactam is important (to suffer from ring strain) if replaced with a 5 or 6-membered ring, which reduces ring strain so less reactive.
Fused with a 6-membered ring to increase ring strain, also a double bond to increase ring strain

2. Structure of Cephalosporin C



. Properties of Cephalosporin C



Disadvantages

- Polar due to the side chain - difficult to isolate and purify
- Low potency - limited to the treatment of urinary tract infections where it is concentrated in the urin He skipped this slide
- Not absorbed orally

Advantages

- Non toxic
- Lower risk of allergic reactions compared to penicillins
- More stable to acid conditions
- More stable to β-lactamases
- Ratio of activity vs Gram -ve and Gram +ve bacteria is better

Conclusion

Useful as a lead compound

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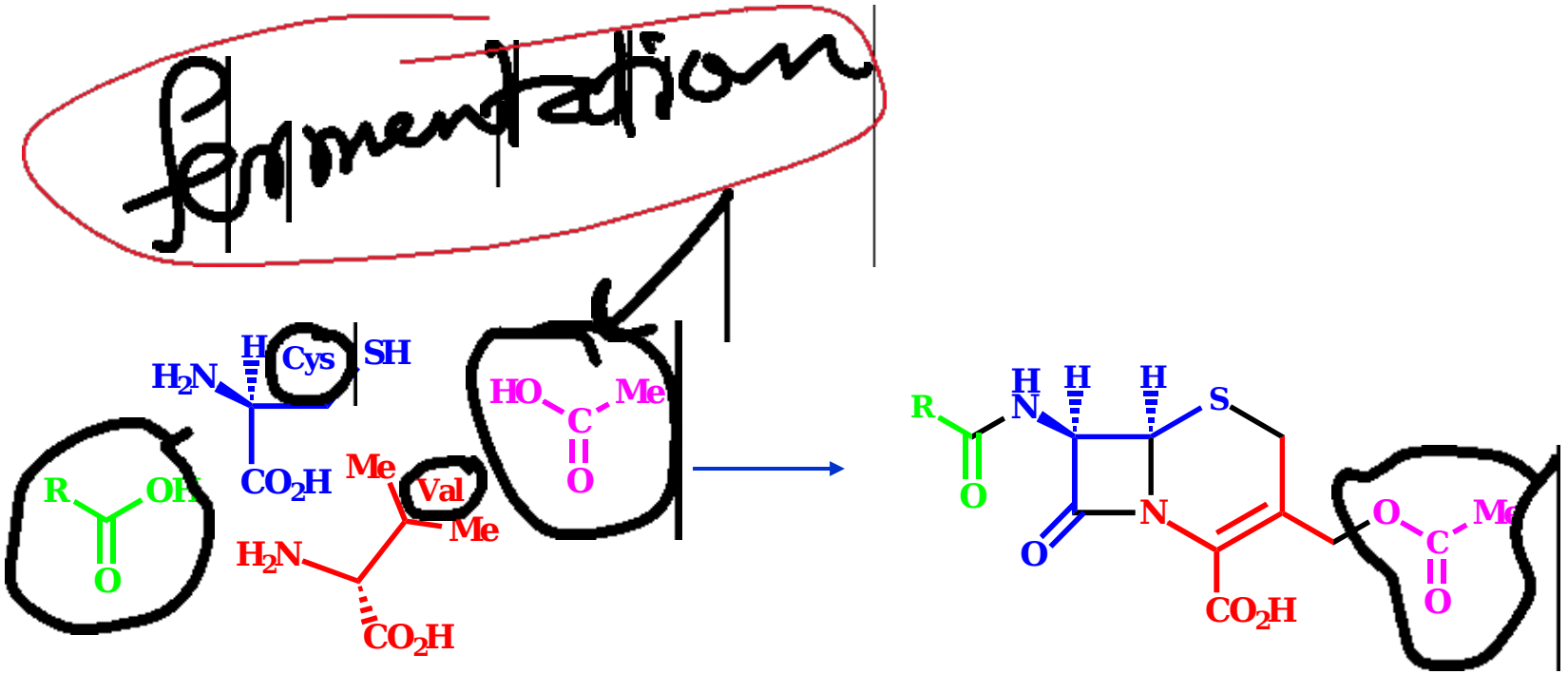
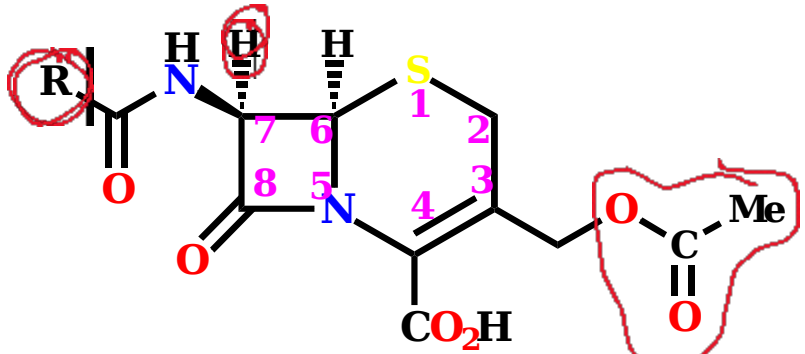
4. Biosynthesis of Cephalosporins



We need to synthesize cephalosporin as follows:

1) One cysteine amino acid
2) One valine amino acid
3) Carboxylic acid to make the acyl side chain
4) Acetic acid to make acetoxy group

5. SAR of Cephalosporins



Similar to penicillins

- The β-lactam ring is crucial to the mechanism
- The carboxylic acid at position 4 is important to binding
- The bicyclic system is important in increasing ring strain
- Stereochemistry is important
- The acetoxy substituent is important to the mechanism

Possible modifications

- 7-Acylamino side chain
- 3-Acetoxymethyl side chain
- Substitution at C-7

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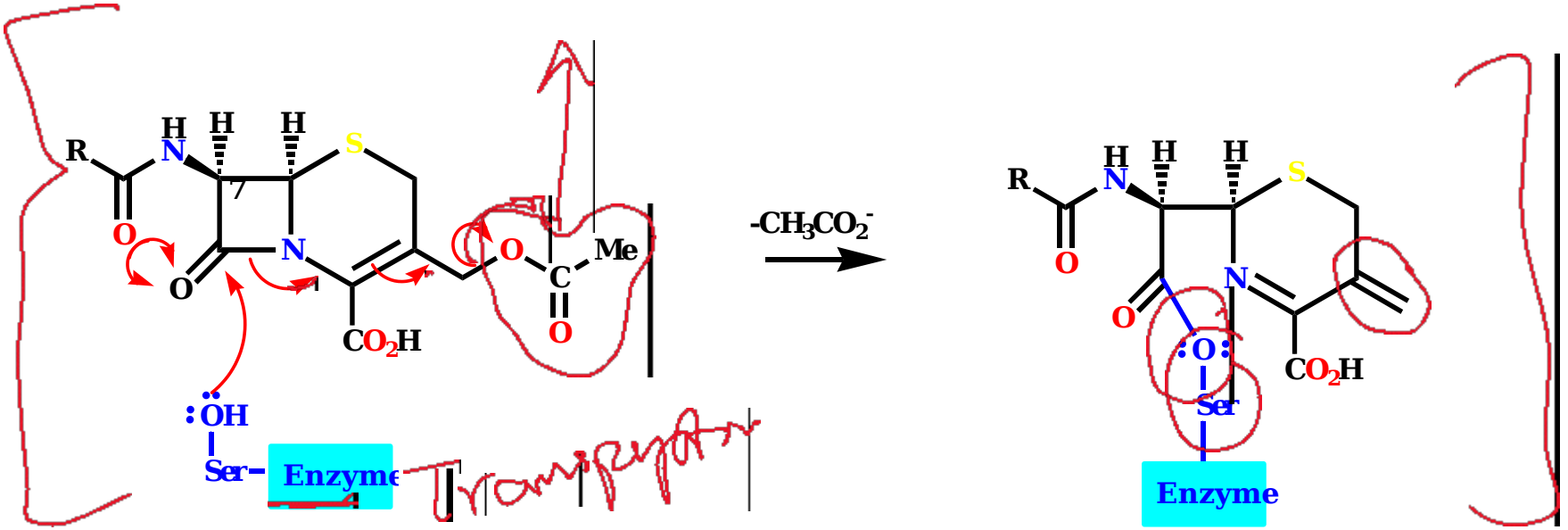
6. Mechanism of Action



- **The acetoxy group acts as a good leaving group and aids the mechanism**

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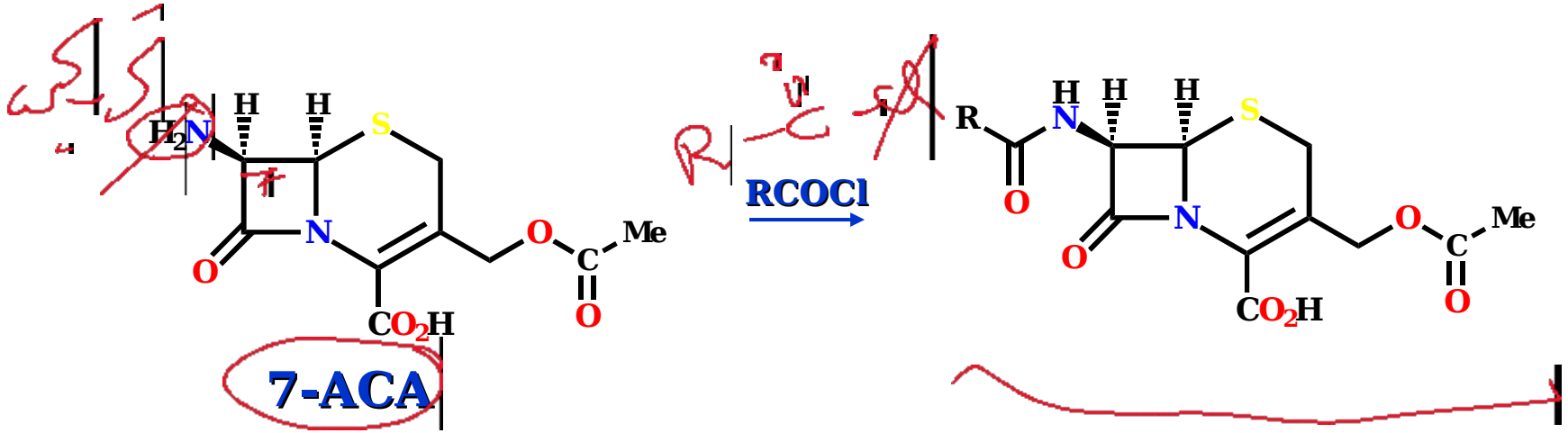
7. Variation of the 7-Acylamino Side Chain

- Not possible to generate analogues by fermentation
- Not possible to generate analogues by a full synthesis
- Restricted to semi-synthetic procedure



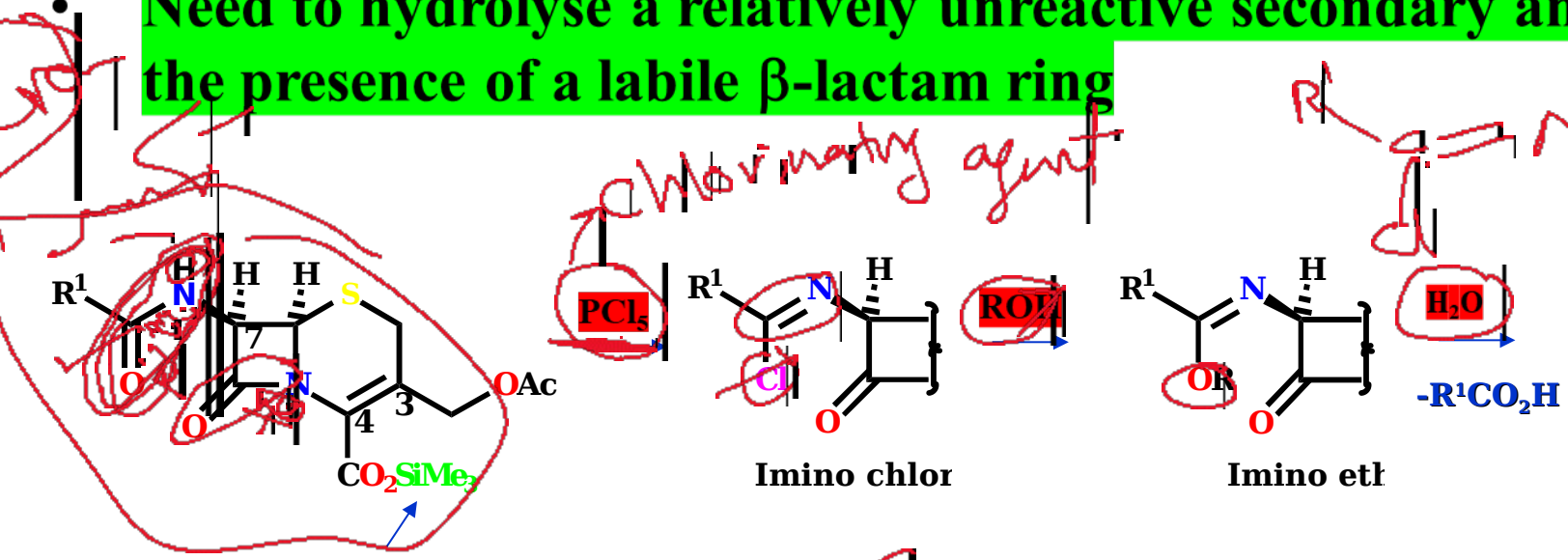
- 7-ACA not available by fermentation
- 7-ACA not available by enzymatic hydrolysis of cephalosporin C

Generated by a chemical hydrolysis

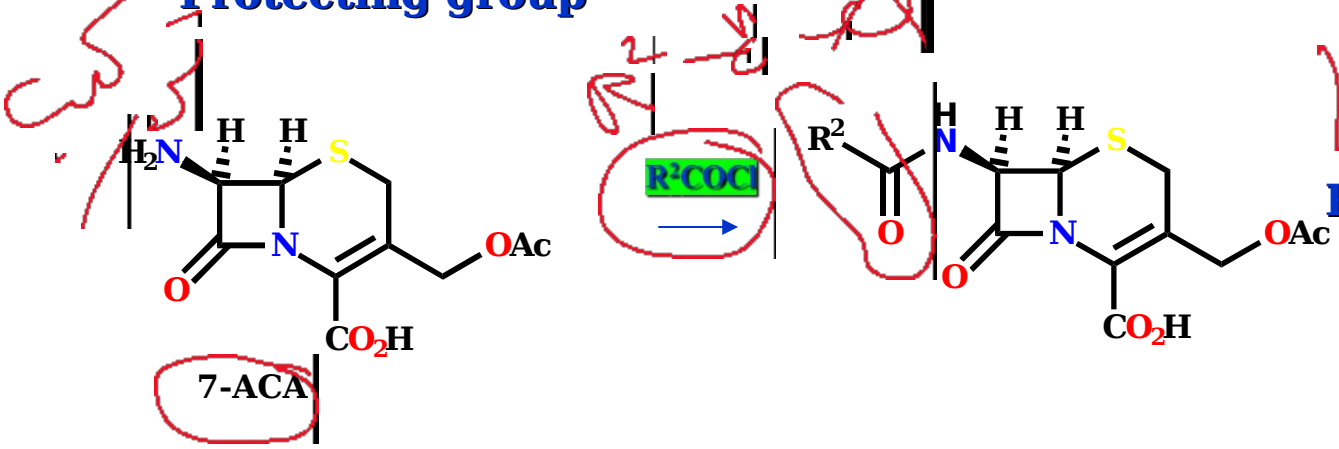
7. Variation of the 7-Acylamino Side Chain

Generation of 7-ACA

- Need to hydrolyse a relatively unreactive secondary amide in the presence of a labile β-lactam ring



Protecting group

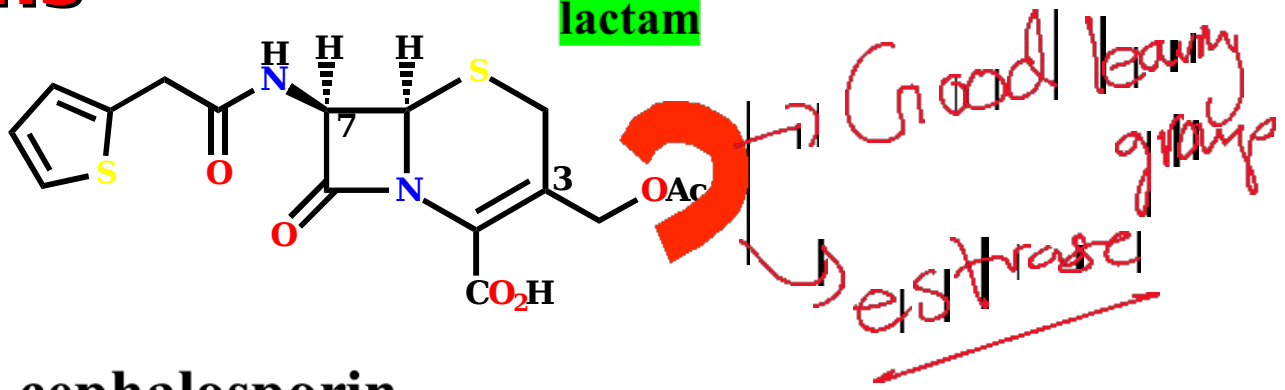


Range of cephalosporins

8. First Generation Cephalosporins

Cephalothin

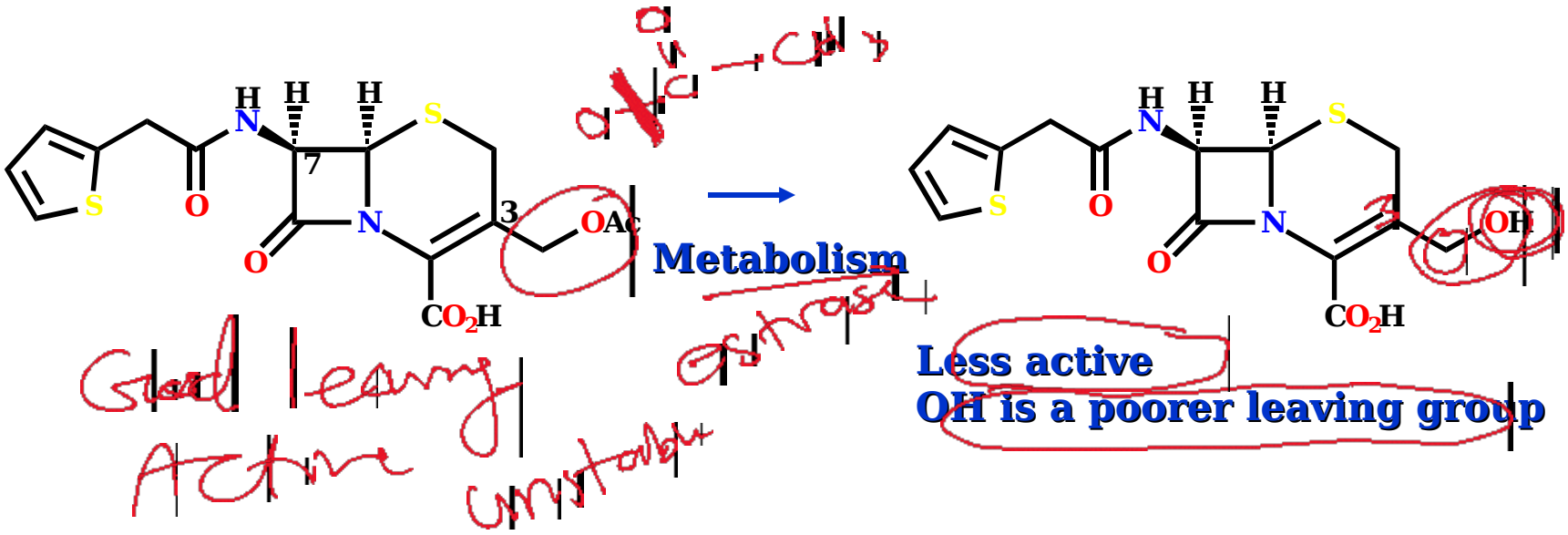
The double bond of cephalosporin increases the ring strain of β-lactam



- First generation cephalosporin
- More active than penicillin G vs. some Gram -ve bacteria
- Less likely to cause allergic reactions
- Useful against penicillinase-producing strains of *S. aureus*
- Not active against *Pseudonomas aeruginosa*
- Poorly absorbed from GIT
- Administered by injection
- Metabolised to give a free 3-hydroxymethyl group (deacetylation)
- Metabolite is less active

8. First Generation Cephalosporins

Cephalothin - drug metabolism

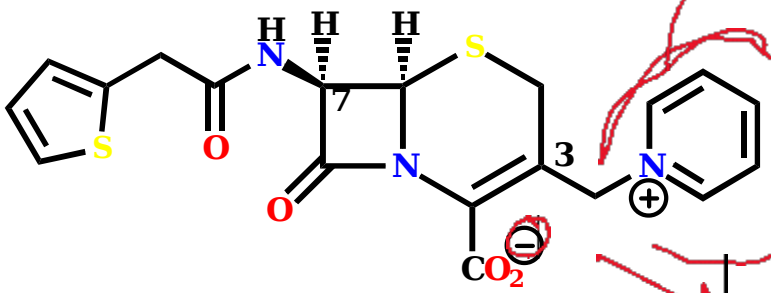


Strategy

- **Replace the acetoxy group with a metabolically stable leaving group**

8. First Generation Cephalosporins

Cephaloridine



- The **pyridine ring is stable to metabolism**
- The **pyridine ring is a good leaving group** (neutralization of charge)
- **Exists as a Zwitterion and is soluble in water**
- **Poorly absorbed through the gut wall**
- **Administered by injection**

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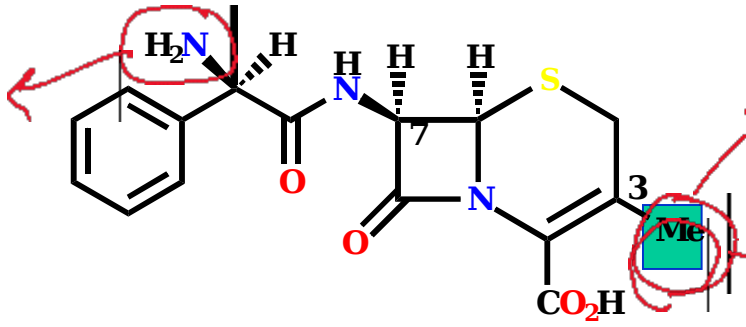
8. First Generation Cephalosporins

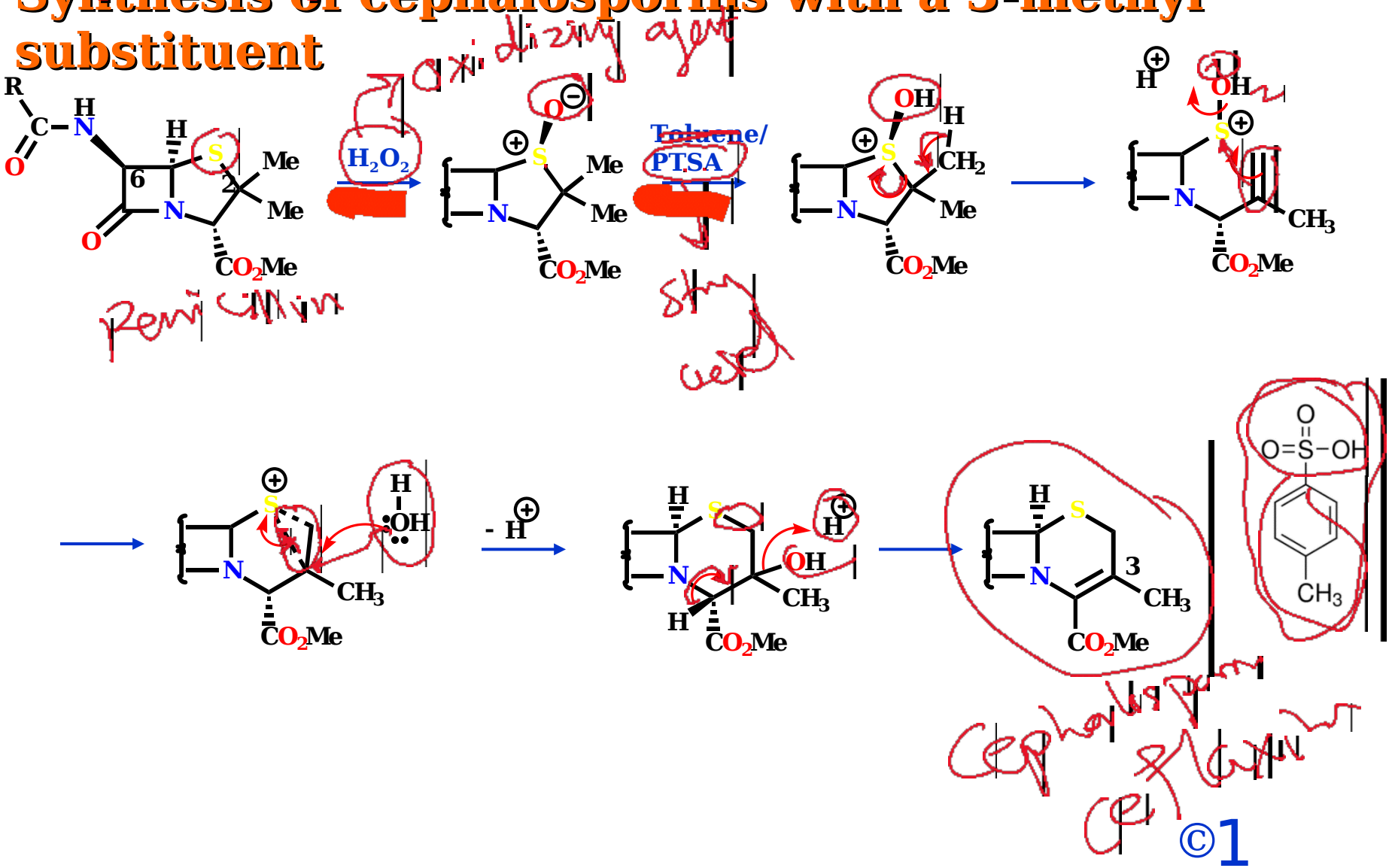
Cefalexin



- The methyl group at position 3 is not a good leaving group
- The methyl group is bad for activity but aids oral absorption – mechanism unknown
- Cefalexin can be administered orally
- A hydrophilic amino group at the α-carbon of the side chain helps to compensate for the loss of activity due to the methyl group

8. First Generation Cephalosporins

Synthesis of cephalosporins with a 3-methyl substituent



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8. First Generation Cephalosporins

Summary

- Generally lower activity than comparable penicillins
- Better range of activity than comparable penicillins
- Best activity is against Gram-positive cocci
- Useful against some Gram-negative infections
- Useful against *S. aureus* and streptococcal infections when penicillins have to be avoided
- Poorly absorbed across the gut wall (except for 3-methyl substituted cephalosporins)
- Most are administered by injection
- Resistance has appeared amongst Gram-negative bacteria (presence of more effective β-lactamases)

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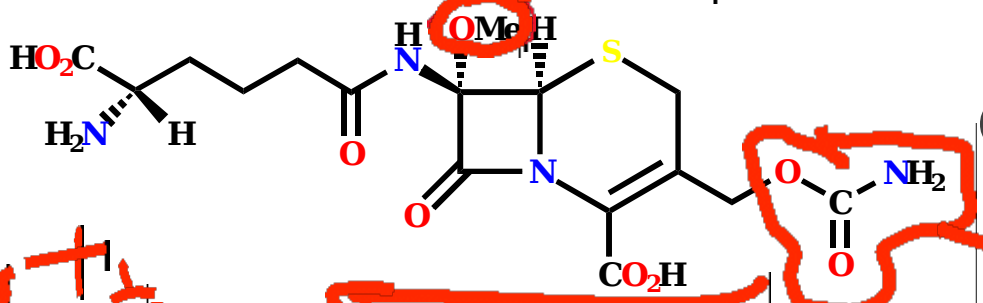
9. Second Generation Cephalosporins

9.1 Cephamycins



Cephamycin C

- Isolated from a culture of ***Streptomyces clavuligerus***
- First β-lactam to be isolated from a bacterial source
- Modifications carried out on the 7-acylamino side chain

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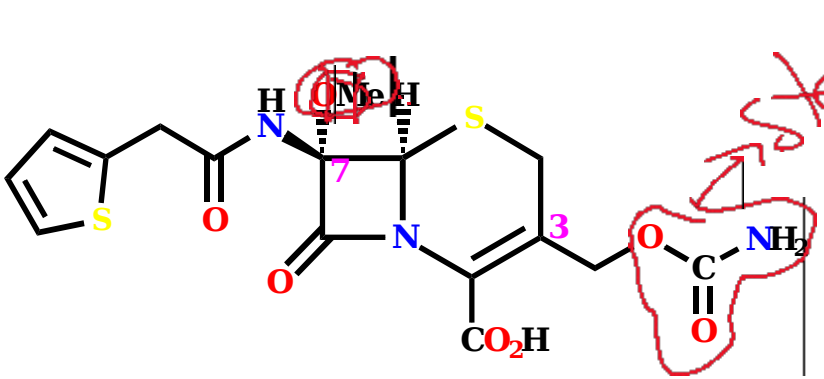
9. Second Generation Cephalosporins

9.1 Cephamycins

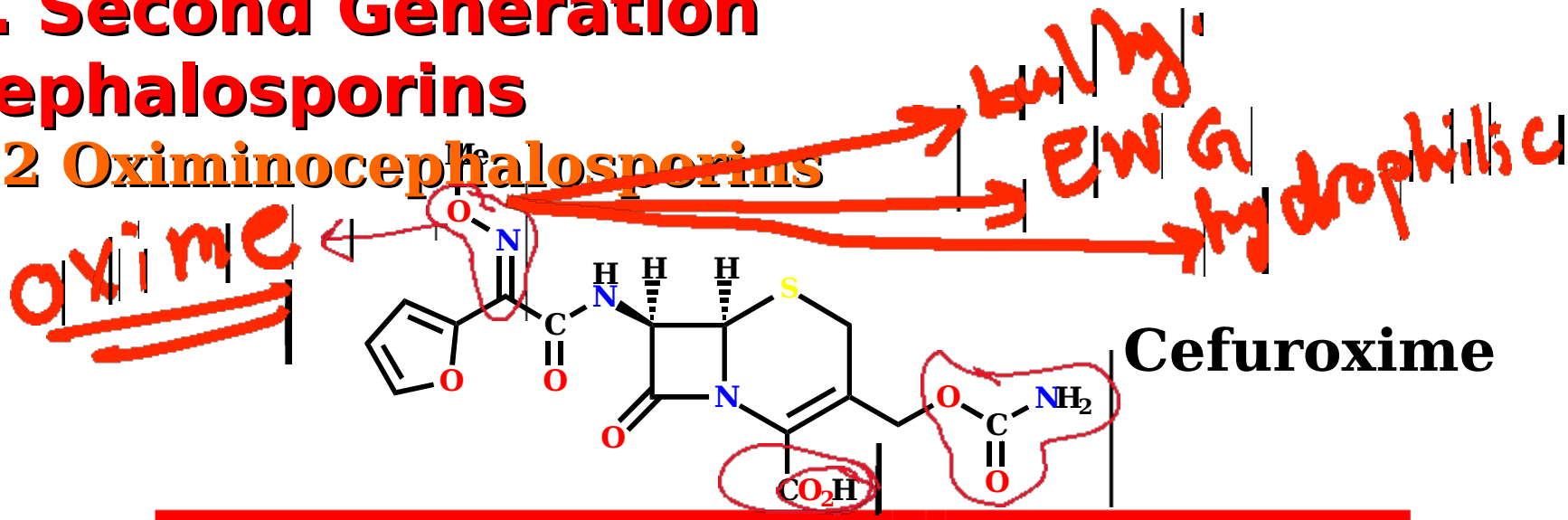


Cefoxitin

- Broader spectrum of activity than most first generation cephalosporins
- Greater resistance to β-lactamase enzymes
- The 7-methoxy group may act as a steric shield
- The urethane group (Carbamate) is stable to metabolism compared to the ester (longer half-life)
- Introducing a methoxy group to the equivalent position of penicillins (position 6) eliminates activity.

9. Second Generation Cephalosporins

9.2 Oximinocephalosporins



Cefuroxime

- Much greater stability against some β-lactamases (oxime)
- Oxime is also withdrawing electrons leading to less electron density on the carbonyl oxygen--→ stability in the stomach acidic pH.
- Resistant to esterases due to the urethane group
- Wide spectrum of activity
- Useful against organisms that have gained resistance to penicillin
- Not active against *P. aeruginosa*
- Used clinically against respiratory infections

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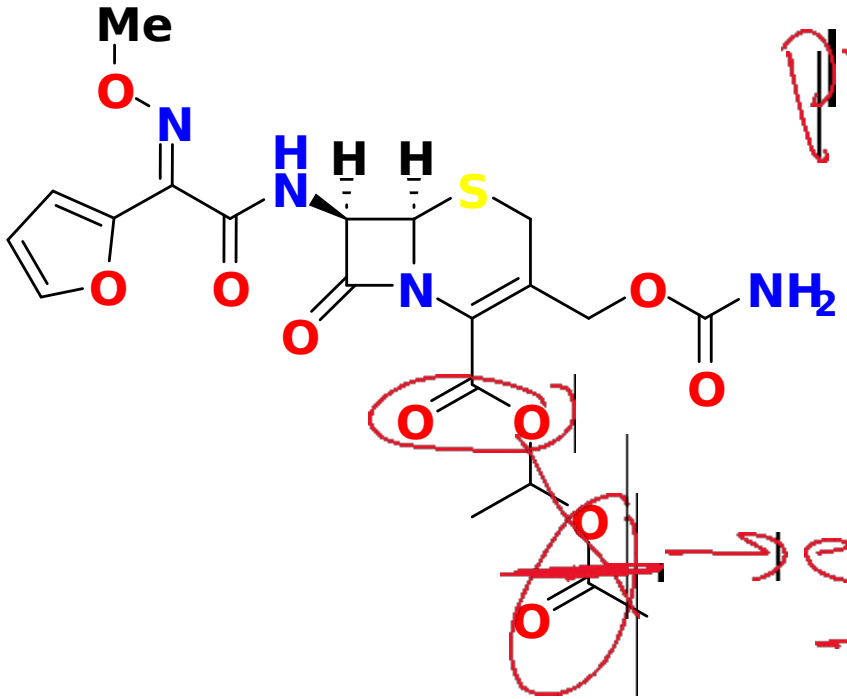
9. Second Generation Cephalosporins

9.2 Oximinocephalosporins

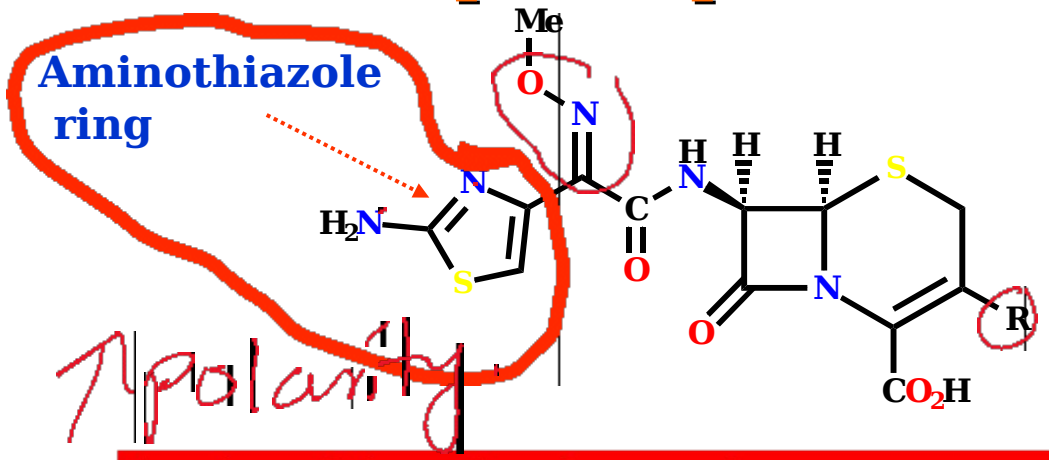


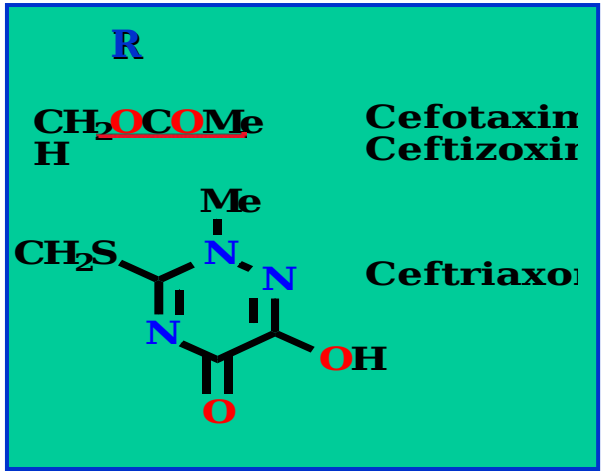
Cefuroxime axetil

- **A prodrug to improve oral bioavailability**
- **Wide spectrum of activity**

10. Third Generation Cephalosporins

Oximinocephalosporins

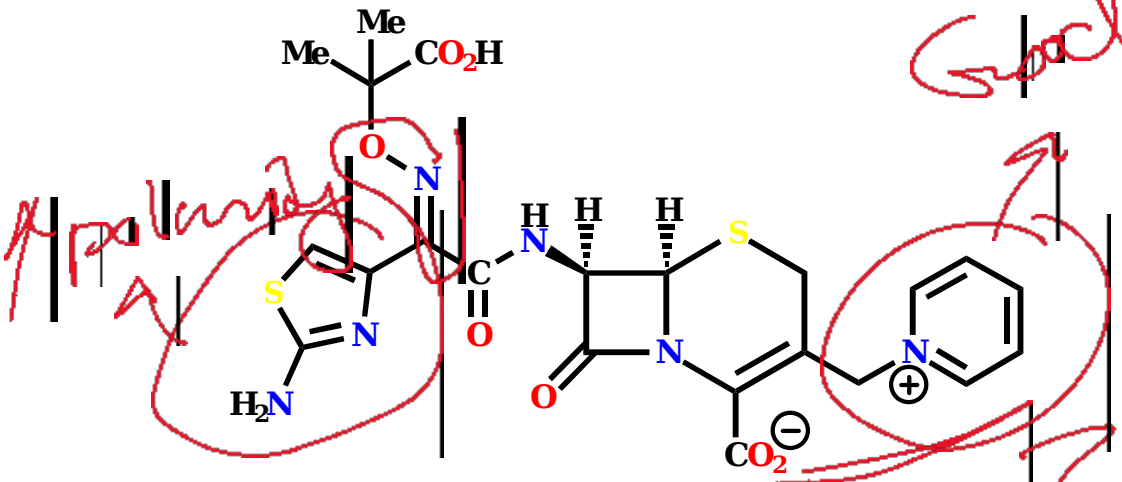




- **Aminothiazole ring enhances penetration of cephalosporins across the outer membrane of Gram -ve bacteria (porin)**
- **May also increase affinity for the transpeptidase enzyme**
- **Good activity against Gram -ve bacteria**
- **Variable activity against Gram +ve cocci**
- **Variable activity vs. *P. aeruginosa***
- **Lack activity vs MRSA**
- **Generally reserved for troublesome infections**

10. Third Generation Cephalosporins

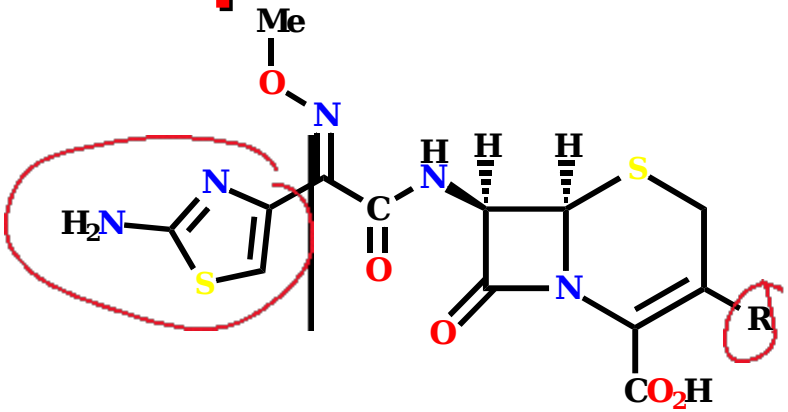
Oximinocephalosporins

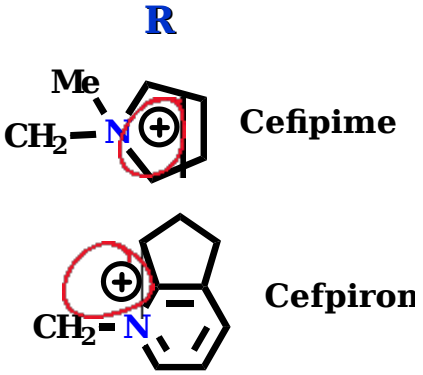


Ceftazidime

- **Injectable cephalosporin**
- **Excellent activity vs. *P. aeruginosa* and other Gram -ve bacteria**
- **Can cross the blood brain barrier**
- **Used to treat meningitis**

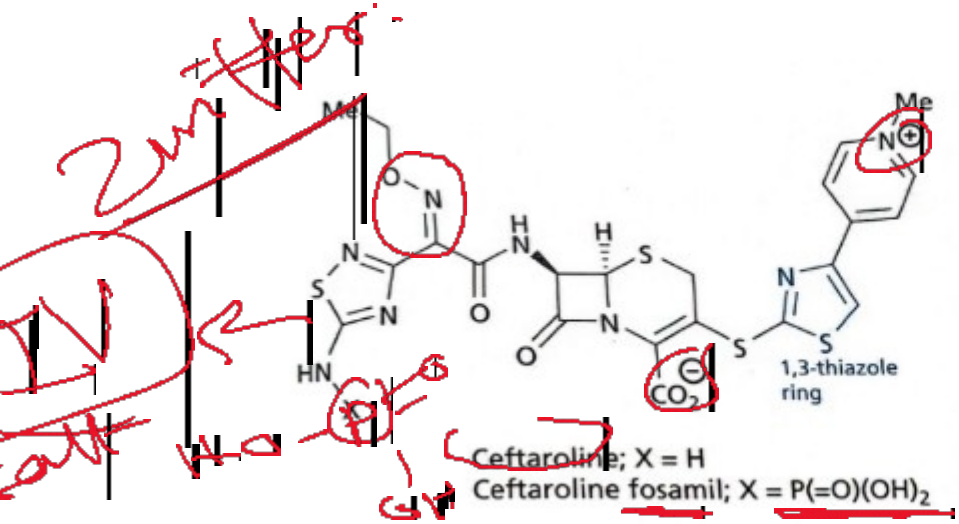
11. Fourth Generation Cephalosporins Oximinocephalosporins

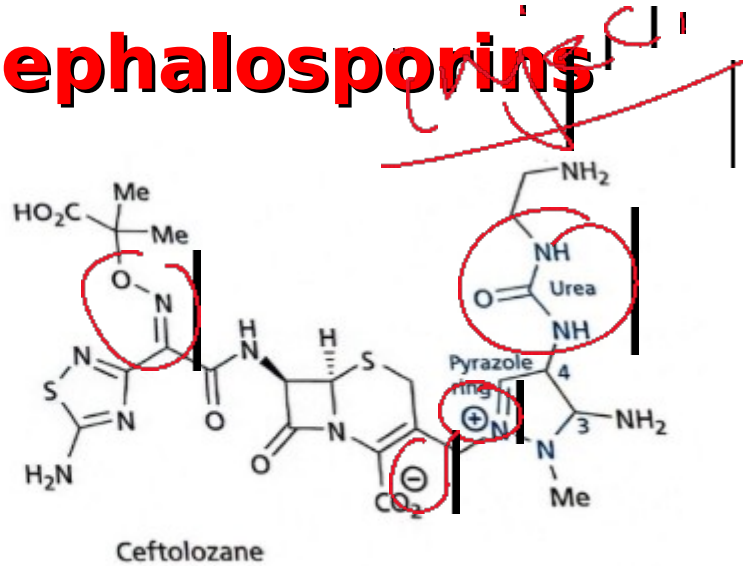




- **Zwitterionic compounds**
- **Enhanced ability to cross the outer membrane of Gram negative bacteria**
- **Good affinity for the transpeptidase enzyme**
- **Low affinity for some β-lactamases**
- **Active vs. Gram +ve cocci and a broad array of Gram -ve bacteria**
- **Active vs. *P. aeruginosa***

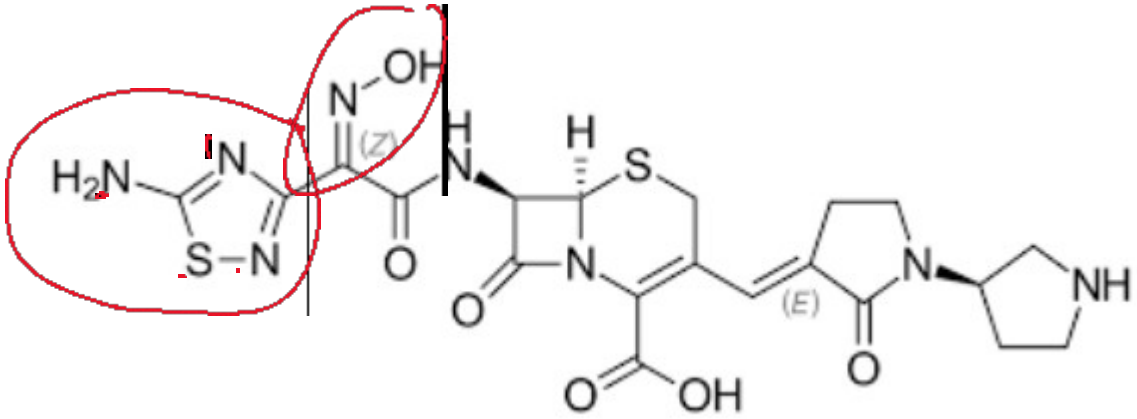
12. Fifth-Generation Cephalosporins





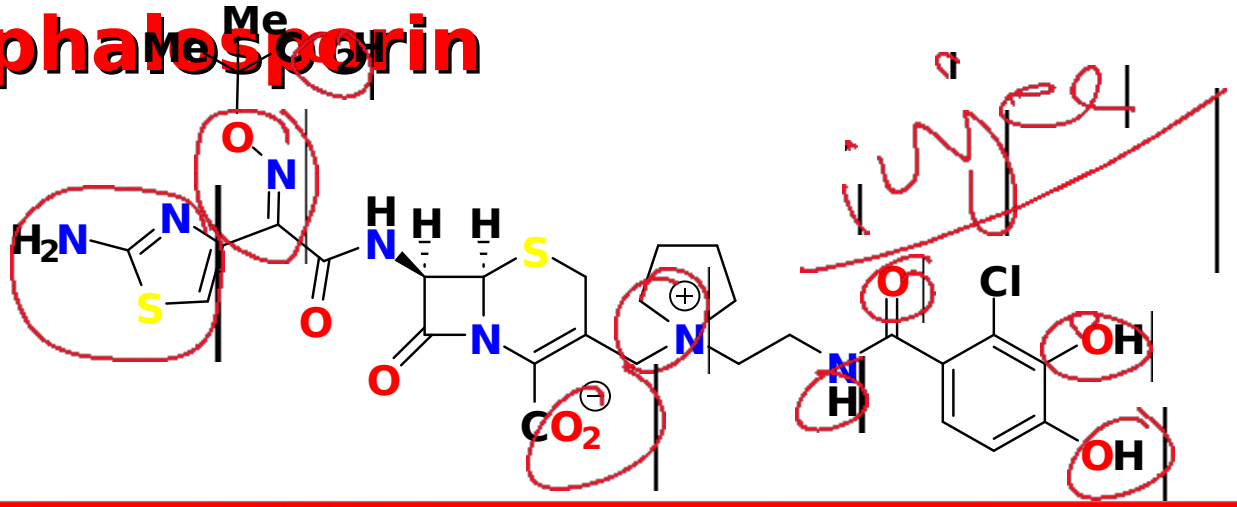
- **Enhanced ability to cross the outer membrane of Gram-negative bacteria (aminothiadiazole).**
- **Resistance against β-lactamases (oxime steric shield).**
- **Ceftaroline fosamil is a water-soluble prodrug of ceftaroline. It gets metabolized *in vivo* by phosphatase enzyme.**
- **Active against MRSA and multi-resistant *Streptococcus pneumonia* (MDRSP).**
- **Active vs. *P. aeruginosa*.**

12. Fifth-Generation Cephalosporins



- **Ceftobiprole**
- **Enhanced ability to cross the outer membrane of Gram-negative bacteria (aminothiadiazole).**
- **Resistance against β-lactamases (oxime steric shield).**
- **Active against hospital-acquired pneumonia and community-acquired pneumonia.**

12. Fifth-Sixth Generation Cephalosporin



Cefiderocol

- **Enhanced ability to cross the outer membrane of Gram-negative bacteria (aminothiazole).**
- **Resistance against β-lactamases (oxime steric shield).**
- **Used to treat complicated urinary tract infections when no other options are available.**
- **It is indicated for the treatment of MDR Gram-negative bacteria including *Pseudomonas aeruginosa*.**
- **It is a siderophore cephalosporin antibiotic, and its iron-chelating ability is a critical part of its mechanism for penetrating Gram-negative bacteria.**

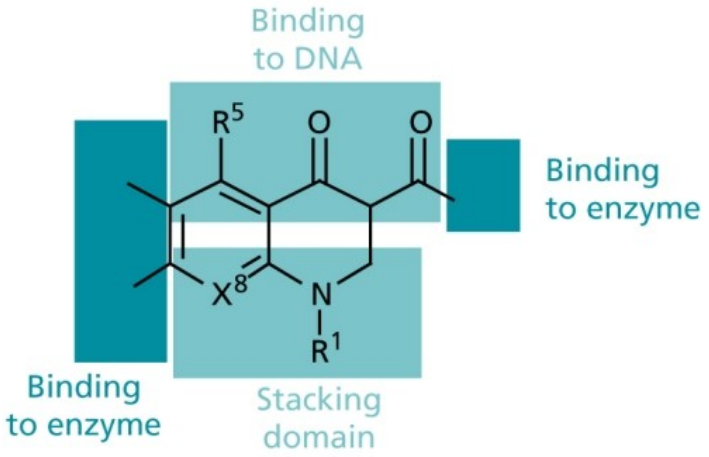
An Introduction to Chemical Basis of Action II

ANTIBACTERIAL AGENTS

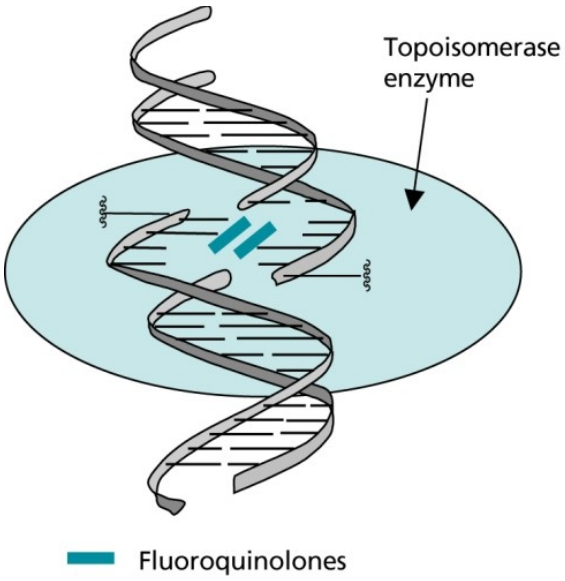
Part 3: Fluroquinolones

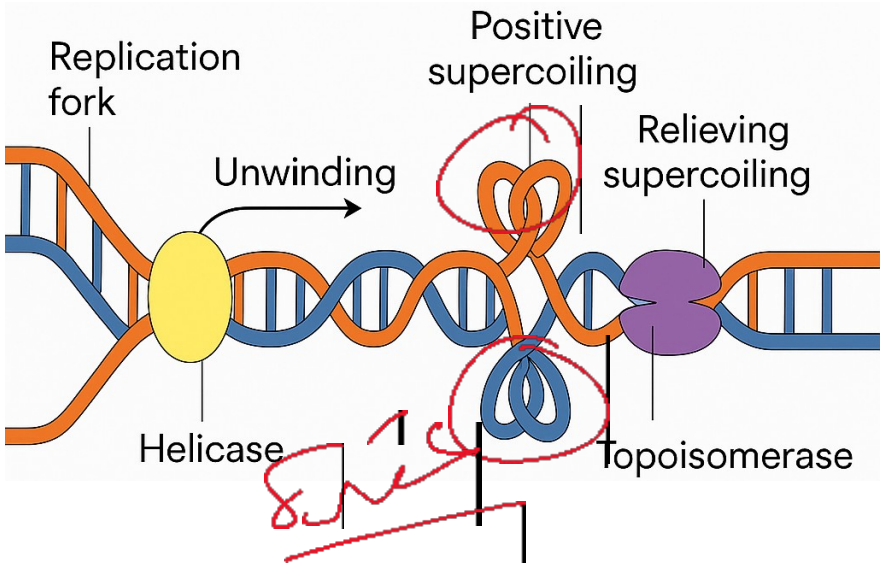
1. Introduction

- **Antibacterial agents which inhibit bacterial nucleic acid transcription and replication**
- **Discovered as a byproduct of chloroquine synthesis in the 1960s**
- **Nalidixic acid was identified in 1962 as the first quinolone antibiotic**



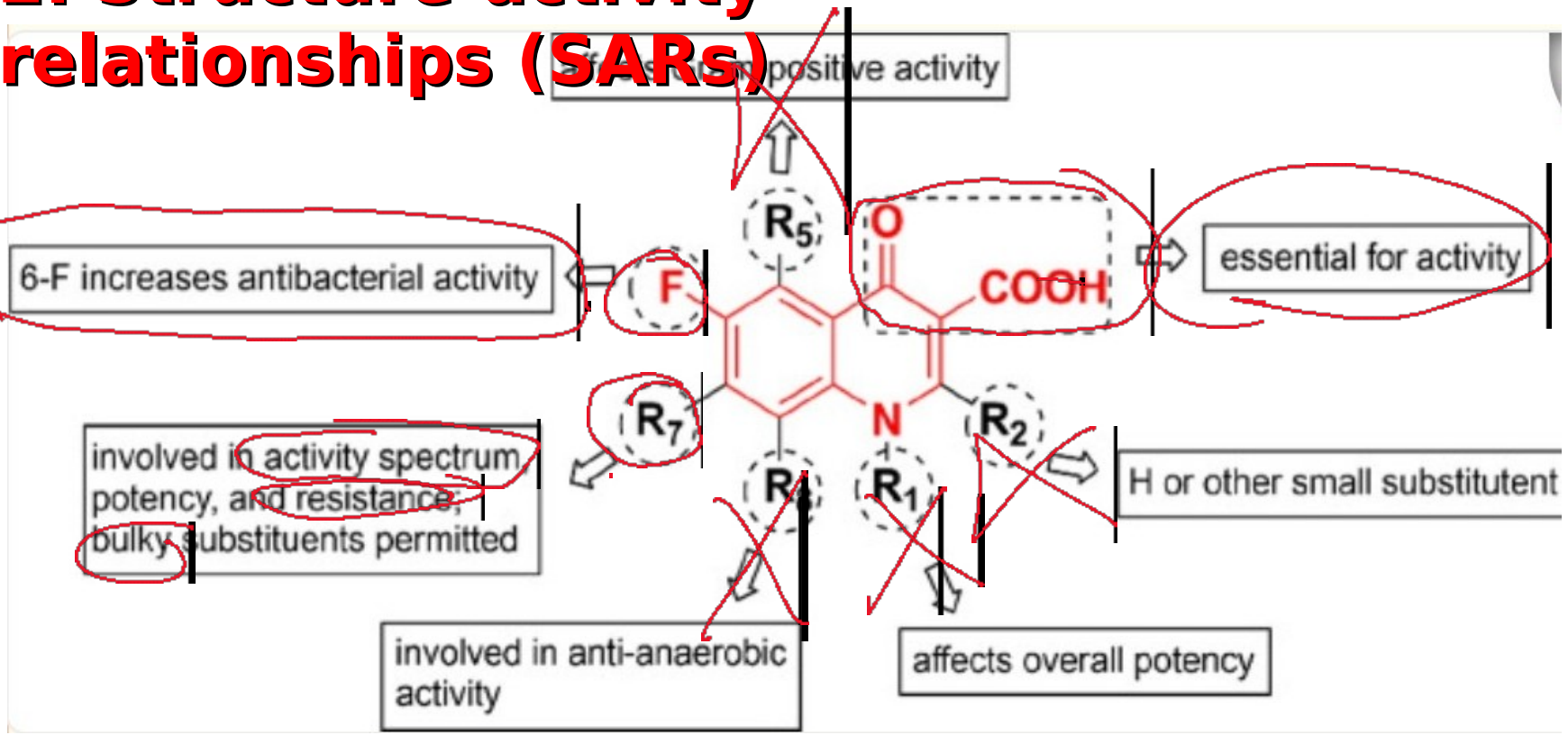
Mechanism of Fluroquinolones





- During replication, helicases unwind the DNA, creating supercoils which are relieved by topoisomerases.
- The created tension is released by topoisomerases, which cut and break both strands of the DNA and rejoin them.
- Fluoroquinones inhibit topoisomerase IV in Gram +ve bacteria with 1000-fold selectivity over a similar human enzyme.
- In Gram -ve bacteria, the topoisomerase II (DNA gyrase) that reintroduces supercoiling after replication and transcription is inhibited.

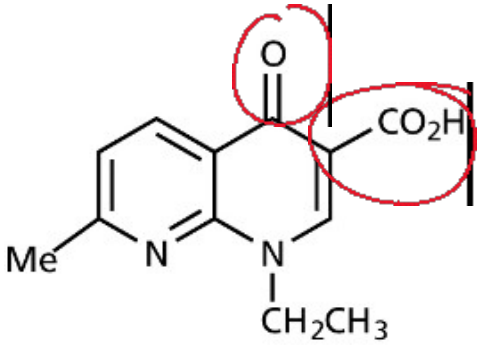
2. Structure-activity relationships (SARs)



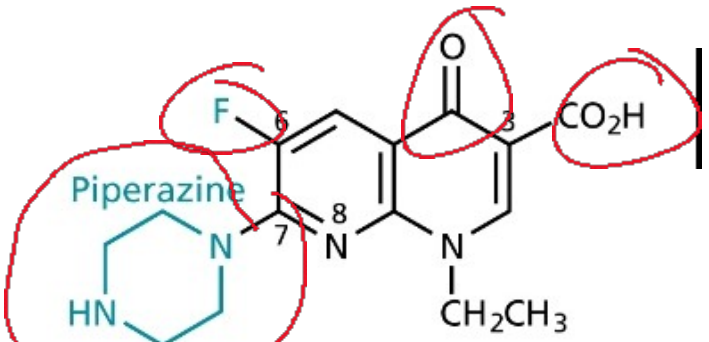
- **Fluorine atom** greatly **increases activity and cellular intake**. However, it is associated with **genotoxicity**.
- **Piperazinyl** or similar rings at **position 7 is beneficial** for a variety of pharmacokinetic reasons (e.g. solubility, UTI treatment). It is also beneficial for **activity against Gram-negative bacteria due to its polarity.**

3. Quinolones and fluoroquinolones

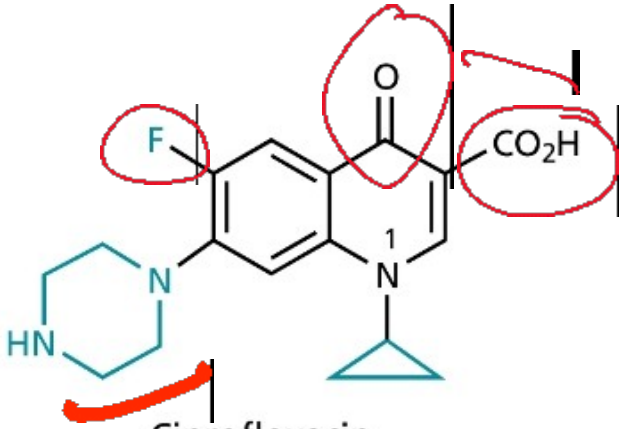
3.1 First generation Fluroquinolones:



Nalidixic acid



Enoxacin

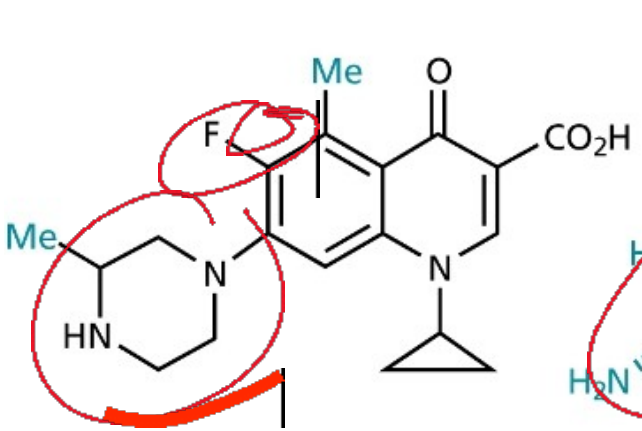


Ciprofloxacin

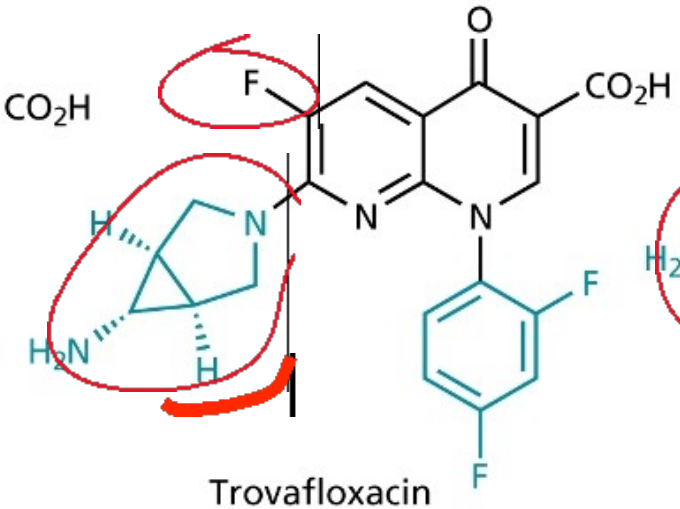
- **Broad-spectrum antibiotics**
- **Inhibit the replication and transcription of bacterial DNA by inhibiting the topoisomerases**
- **Used for infections involving the urinary, respiratory and gastrointestinal tracts as well as against infections of skin, bone and joints**

3. Quinolones and fluoroquinolones

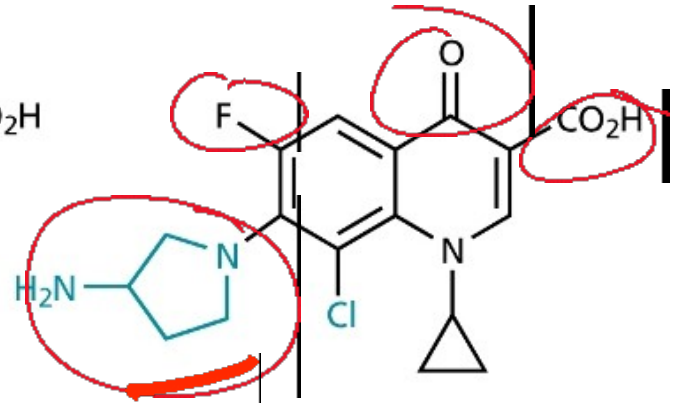
3.2 Second generation Fluroquinolones:



Grepafloxacin



Trovafloxacin

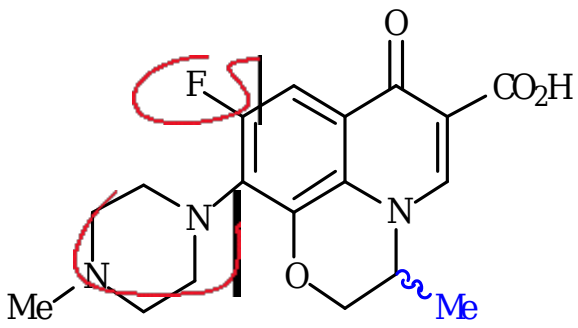


Clinafloxacin

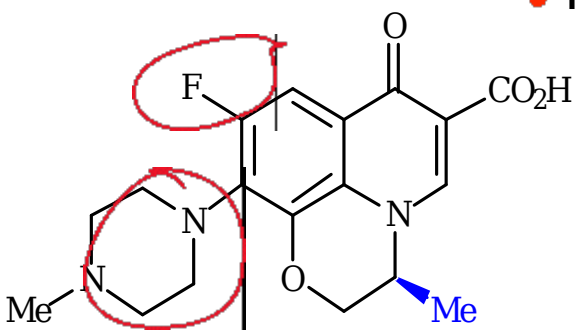
- **2nd Generation has a broader spectrum of activity than 1st Generation**
- **Grepafloxacin had been withdrawn because of cardiac side effects**

3. Quinolones and fluoroquinolones

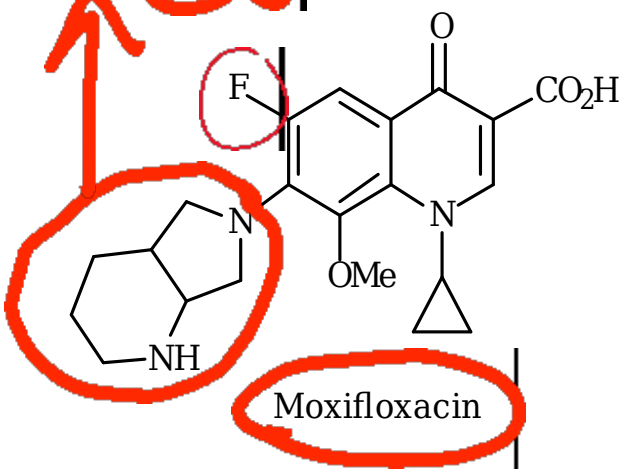
3.3 Third generation Fluroquinolones:



Ofloxacin



Levofloxacin

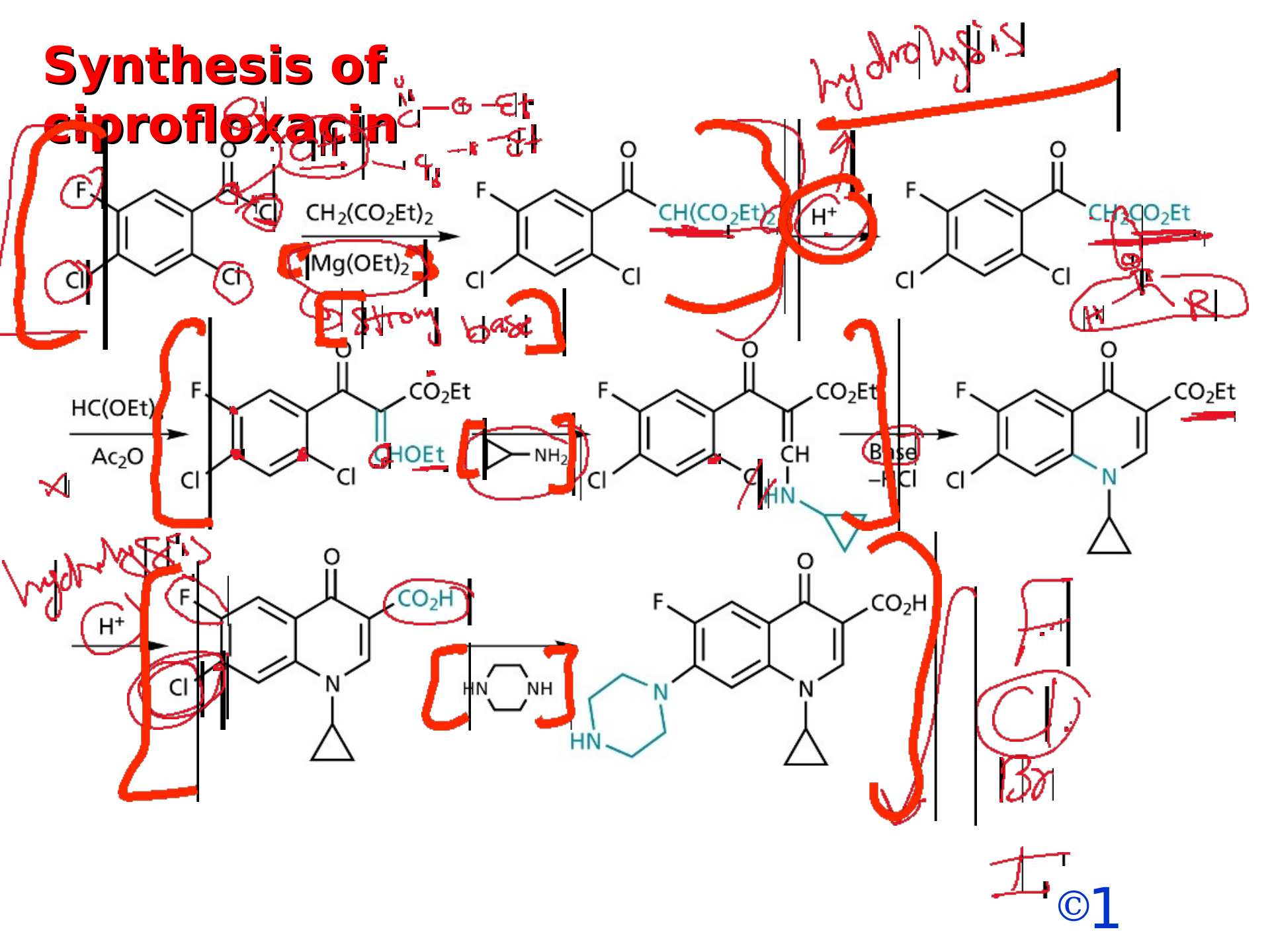


Moxifloxacin

Figure 19.73 Third generation fluoroquinolones.

- **The bulky bicyclic substituent at position 7 of moxifloxacin and similar analogues is thought to make these agents less susceptible to efflux mechanisms involving a multidrug transport protein.**

Synthesis of ciprofloxacin



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